

CAFFEINE INTAKE AND THE RISK OF FIRST-TRIMESTER SPONTANEOUS ABORTION

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ABSTRACT

Background Some epidemiologic studies have suggested that the ingestion of caffeine increases the risk of spontaneous abortion, but the results have been inconsistent.

Methods We performed a population-based, case-control study of early spontaneous abortion in Uppsala County, Sweden. The subjects were 562 women who had spontaneous abortion at 6 to 12 completed weeks of gestation (the case patients) and 953 women who did not have spontaneous abortion and were matched to the case patients according to the week of gestation (controls). Information on the ingestion of caffeine was obtained from in-person interviews. Plasma cotinine was measured as an indicator of cigarette smoking, and fetal karyotypes were determined from tissue samples. Multivariate analysis was used to estimate the relative risks associated with caffeine ingestion after adjustment for smoking and symptoms of pregnancy such as nausea, vomiting, and tiredness.

Results Among nonsmokers, more spontaneous abortions occurred in women who ingested at least 100 mg of caffeine per day than in women who ingested less than 100 mg per day, with the increase in risk related to the amount ingested (100 to 299 mg per day: odds ratio, 1.3; 95 percent confidence interval, 0.9 to 1.8; 300 to 499 mg per day: odds ratio, 1.4; 95 percent confidence interval, 0.9 to 2.0; and 500 mg or more per day: odds ratio, 2.2; 95 percent confidence interval, 1.3 to 3.8). Among smokers, caffeine ingestion was not associated with an excess risk of spontaneous abortion. When the analyses were stratified according to the results of karyotyping, the ingestion of moderate or high levels of caffeine was found to be associated with an excess risk of spontaneous abortion when the fetus had a normal or unknown karyotype but not when the fetal karyotype was abnormal.

Conclusions The ingestion of caffeine may increase the risk of an early spontaneous abortion among non-smoking women carrying fetuses with normal karyotypes. (N Engl J Med 2000;343:1839-45.)

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CAFFEINE is a naturally occurring compound that is metabolized more slowly in pregnant women than in nonpregnant women.¹ Caffeine passes readily through the placenta to the fetus,¹ but the biologic mechanisms by which caffeine could induce a spontaneous abortion are not known.^{2,3} The results of epidemiologic studies relating the ingestion of caffeine to the risk of spontaneous abortion have been inconclusive,⁴⁻¹³ partly because the relation between the consumption of coffee (usually the primary source of caffeine), symptoms of pregnancy (such as nausea or aversion to the odor or taste of coffee), and fetal viability is complex. In response to such symptoms, many women decrease their ingestion of caffeine during pregnancy. Because the symptoms are more common among women with viable pregnancies than among those with nonviable pregnancies, the ingestion of caffeine in early pregnancy may reflect, rather than affect, fetal viability.^{6,14} Most previous studies have not included in their analyses data on symptoms of pregnancy,^{4,5,8,11-13} and the few that have included these data have used fairly insensitive markers, such as the presence or absence of nausea or vomiting at any time during pregnancy.^{6,7,9,10} Moreover, only one study with a sufficient sample size focused on the first trimester of pregnancy,¹² when changes in caffeine intake, pregnancy-related symptoms, and the majority of spontaneous abortions occur.

In epidemiologic studies, the range of caffeine ingestion has been narrow.^{5-8,10,11,13} Moreover, the assessment of exposure has been suboptimal, with the reporting of caffeine intake occurring long after the period in question or with little regard to changes in ingestion during pregnancy.^{4-6,8-10,12,13} Finally, studies of caffeine ingestion and spontaneous abortion have, with one exception,¹⁰ not distinguished between chromosomally normal and abnormal fetuses.

In Sweden, the consumption of coffee is high, and health care coverage is nationwide; it was therefore possible to investigate whether caffeine is associated with an elevated risk of early spontaneous abortion

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in the general population. The current study was designed to analyze caffeine intake, smoking status, symptoms of pregnancy, and the risk of spontaneous abortion. In addition, fetal tissue, when available, was collected for chromosomal analysis.

METHODS

Study Subjects

The study was conducted in Uppsala County, Sweden, from 1996 through 1998. Cases of spontaneous abortion were identified at the Department of Obstetrics and Gynecology of Uppsala University Hospital, which is the only place in the county for the care of women with spontaneous abortions. During this period, we identified as potential case patients 652 women with spontaneous abortions who presented at the department at 6 to 12 completed weeks of gestation and whose pregnancies had been confirmed by a positive test.¹⁵ Of these women, 562 (86 percent) agreed to participate. Among the 293 women in whom chorionic villi were identified in tissue obtained at curettage, karyotyping was successful in 258 (88 percent). Chromosomes were studied with the use of G-banding, and 11 cells in metaphase were routinely analyzed¹⁶; karyotyping was considered unsuccessful if fewer than 3 cells in metaphase were obtained. Karyotype analysis revealed that 101 fetuses (58 male and 43 female) were chromosomally normal and 157 (72 male, 63 female, 16 with triploidy, and 6 with tetraploidy) were abnormal.

The control subjects were selected primarily from the antenatal care clinics in Uppsala County. They were frequency-matched to the women who had had spontaneous abortions with regard to duration of gestation (in completed weeks) and area of residence (one of the five municipalities in the county). Of the 1037 women who were seeking antenatal care and were asked to participate, 953 (92 percent) agreed to do so. All potential control subjects underwent vaginal ultrasonography before the interview. If a nonviable intrauterine pregnancy was detected, the woman was recruited as a member of the group with spontaneous abortion (this occurred in 53 of the 562 case patients).

In Uppsala County, there are approximately 3 legally induced abortions for every 10 completed pregnancies, and some of these terminated pregnancies would have resulted in spontaneous abortion if the pregnancy had continued. To limit bias in the selection of control subjects, women with induced abortions were added to the control group. In total, 310 women who had undergone induced abortions were asked to participate, and 273 (88 percent) agreed to do so. In these supplementary analyses, women with induced abortions were added to the control group according to the distribution of the length of gestation of induced abortions in Uppsala County during the study period.

Collection of Data

Three midwives conducted in-person interviews with the women with spontaneous abortion and the control subjects recruited among patients receiving antenatal care, using a structured questionnaire, and two doctors conducted interviews with the control subjects in whom abortions had been induced. Ninety percent of the case patients were interviewed within two weeks after the diagnosis of spontaneous abortion, and all were interviewed within seven weeks. All control subjects were interviewed in early pregnancy, within six days after their completed week of gestation used in matching. To avoid delay and to limit nonparticipation, 50 women who had had spontaneous abortion and 5 control subjects were interviewed by telephone.

All the women were asked to report specific sources of caffeine ingested daily on a week-by-week basis, starting four weeks before the last menstrual period and ending in the most recently completed week of gestation. Sources of caffeine included coffee (brewed, boiled, instant, and decaffeinated), tea (loose tea, tea bags, and herbal tea), cocoa, chocolate, soft drinks, and caffeine-containing medications. Respondents were offered four cup sizes from which

to choose (1.0 dl, 1.5 dl, 2.0 dl, and 3.0 dl). Weekly consumption of soft drinks was estimated by the women in centiliters. We estimated the intake of caffeine using the following conversion factors: for 150 ml of coffee, 115 mg of caffeine if it was brewed, 90 mg if boiled, and 60 mg if instant; for 150 ml of tea, 39 mg if it was loose tea or a tea bag and 0 mg if herbal tea; for 150 ml of soft drinks (cola), 15 mg; for 150 ml of cocoa, 4 mg; and for 1 g of chocolate (bar), 0.3 mg. A few medications included 50 to 100 mg of caffeine per tablet.¹⁷ Of all caffeine ingested, coffee accounted for 76 percent, tea for 23 percent, and other sources for 1 percent. None of the women ingested decaffeinated coffee predominantly. The mean daily amount of caffeine ingested was calculated from the time of estimated conception (two weeks after the last menstrual period) through the most recently completed week of gestation.

Plasma cotinine was measured by gas chromatography with use of *N*-ethylnorcotinine as an internal standard.¹⁸ Blood samples for the measurement of cotinine were obtained from the case patients at the time of spontaneous abortion and from the control subjects at the time they were interviewed. We defined smokers as women who had a plasma cotinine concentration of more than 15 ng per milliliter¹⁹; for 23 women whose plasma cotinine values were missing, we used self-reported daily smoking during all weeks of pregnancy.

We determined scores for symptoms related to pregnancy for each week of gestation by assigning a score for nausea (0, never; 1, sometimes but not daily; 2, daily but not all day; 3, daily all day), vomiting (0, never; 1, sometimes but not daily; 2, daily), and fatigue (0, no; 1, yes but with unchanged sleeping habits; 2, yes with slightly changed sleeping habits; 3, yes with pronounced change in sleeping habits). We then calculated the average weekly score for each symptom. We also collected data on other potential risk factors.

Oral informed consent was obtained from all the women, and the study was approved by the ethics committee of the medical faculty at Uppsala University.

Statistical Analysis

Data were analyzed with the use of conditional logistic-regression analysis, matched for the week of gestation. Since the study was frequency-matched, all controls were considered in the subanalyses of risks of spontaneous abortion according to fetal karyotype. Variables were included in the multivariate analyses if they were judged, a priori, to be potential confounders or if they changed the estimates of the effect of caffeine by more than 5 percent. Whenever we assessed the odds ratios for categories of caffeine intake, we performed a test for trend with the categories of caffeine intake as an ordinal scale.

RESULTS

The mean prepregnancy intake of caffeine was similar in the women who had spontaneous abortion and the control subjects (346 mg and 329 mg per day, respectively; $P=0.20$). The women who had spontaneous abortion were significantly older than the control subjects, were more likely to have been born outside the Nordic countries (Sweden, Denmark, Norway, Finland, and Iceland), and were more likely to have had previous pregnancies and previous spontaneous abortions ($P<0.001$ for each comparison) (Table 1).

During early pregnancy, the women who had spontaneous abortion had a significantly higher caffeine intake than the control subjects ($P<0.001$), and more of them were smokers ($P<0.001$). Nausea (with or without vomiting) and tiredness as symptoms of pregnancy were more prevalent and severe among the control subjects ($P<0.001$ for both comparisons). There were no significant differences between the two groups

TABLE 1. CHARACTERISTICS OF THE WOMEN WITH SPONTANEOUS ABORTION (CASE PATIENTS) AND THE CONTROL SUBJECTS.*

CHARACTERISTIC	CASE PATIENTS	CONTROL SUBJECTS
	(N=562)	(N=953)
	number (percent)	
Age		
≤19 yr	5 (1)	4 (<1)
20–29 yr	224 (40)	543 (57)
30–34 yr	175 (31)	317 (33)
≥35 yr	158 (28)	89 (9)
No. of previous pregnancies		
0	122 (22)	307 (32)
≥1	440 (78)	646 (68)
No. of previous spontaneous abortions		
0	393 (70)	775 (81)
≥1	169 (30)	178 (19)
Country of birth		
Sweden, Norway, Denmark, Finland, or Iceland	507 (90)	908 (95)
Other	55 (10)	45 (5)
Mean daily intake of caffeine during pregnancy†		
0–99 mg	116 (21)	307 (32)
100–299 mg	210 (37)	378 (40)
300–499 mg	140 (25)	184 (19)
≥500 mg	96 (17)	84 (9)
Intake of alcohol during the preceding week‡		
0 ml	457 (81)	787 (83)
1–99 ml	85 (15)	157 (16)
≥100 ml	20 (4)	9 (1)
Smoking status		
Nonsmoker	401 (71)	811 (85)
Smoker§	115 (20)	121 (13)
Data missing	46 (8)	21 (2)
Nausea or vomiting¶		
Never	257 (46)	153 (16)
Sometimes or daily	305 (54)	800 (84)
Tiredness¶		
No	110 (20)	69 (7)
Yes	452 (80)	884 (93)
Change in eating habits		
No	263 (47)	229 (24)
Yes	299 (53)	724 (76)
Aversion to any food or beverage		
No	357 (64)	328 (34)
Yes	205 (36)	623 (65)
Data missing	0	2 (<1)
Aversion to coffee		
No	444 (79)	560 (59)
Yes	118 (21)	393 (41)
Week of gestation		
6	32 (6)	53 (6)
7	59 (10)	95 (10)
8	66 (12)	103 (11)
9	97 (17)	162 (17)
10	127 (23)	210 (22)
11	109 (19)	200 (21)
12	72 (13)	130 (14)

*Because of rounding, not all percentages total 100.

†Intake was estimated on a week-by-week basis from the estimated date of conception to the end of the last completed week of gestation before the interview.

‡The amounts were recalculated to correspond to a volume of 40 percent alcohol.

§The criterion for classification as a smoker was a plasma cotinine value above 15 ng per milliliter or daily smoking during pregnancy.

¶The responses were based on the highest level during any week of pregnancy.

with regard to education, prepregnancy body-mass index, participation in shift work, or use of vitamin supplements during pregnancy (data not shown).

The severity of nausea (according to the mean severity score) and the mean daily intake of caffeine in the women with spontaneous abortion and the control subjects are shown in Figure 1 as a function of the week of gestation. At four weeks after the last menstrual period, there was a marked decrease in the ingestion of caffeine in both groups, but the decline was much more pronounced in the control group. The declining intake of caffeine coincided with an increase in the proportion of women who had nausea, which was also more pronounced among the control subjects than among the women who had spontaneous abortion.

In multivariate analyses, which included caffeine intake, smoking status, age, number of previous pregnancies, history of spontaneous abortion, consumption of alcohol, and presence or absence of nausea, vomiting, and fatigue, the adjusted odds ratios for spontaneous abortion in women who ingested at least 100 mg of caffeine per day, as compared with women who ingested less than 100 mg of caffeine per day, were as follows: 100 to 299 mg per day — odds ratio, 1.3 (95 percent confidence interval, 0.9 to 1.7); 300 to 499 mg per day — odds ratio, 1.5 (95 percent confidence interval, 1.0 to 2.1); and 500 mg or more per day — odds ratio, 1.4 (95 percent confidence interval, 0.9 to 2.2) (P for trend = 0.05). For smokers as compared with nonsmokers, the adjusted odds ratio was 1.5 (95 percent confidence interval, 1.1 to 2.1). However, there was a significant interaction between caffeine ingestion and smoking with regard to the risk of spontaneous abortion (P < 0.001), so further analyses were stratified according to smoking status. Among smokers, the ingestion of caffeine was not associated with an excess risk of spontaneous abortion, whereas among nonsmokers, high intake of caffeine (at least 500 mg per day) was associated with a doubling in risk (Table 2). A repetition of the adjusted regression analysis to include control subjects in whom abortions were induced had little effect on the results (data not shown).

With regard to symptoms of pregnancy, we did not include aversion to coffee in the multivariate analysis because of its high degree of inverse correlation with caffeine ingestion. When we restricted the analysis to nonsmokers who reported no such aversion, the caffeine-related risk of spontaneous abortion increased (Table 2). Moreover, because coffee was the main source of caffeine, the possibility of confounding by other constituents in coffee also existed. When we assessed the risk of spontaneous abortion according to the level of caffeine ingestion among non-coffee drinkers and nonsmokers, the caffeine-related odds ratios increased, but the confidence intervals were wide. For smokers, there was no effect of caffeine ingestion in any of these analyses (data not shown).

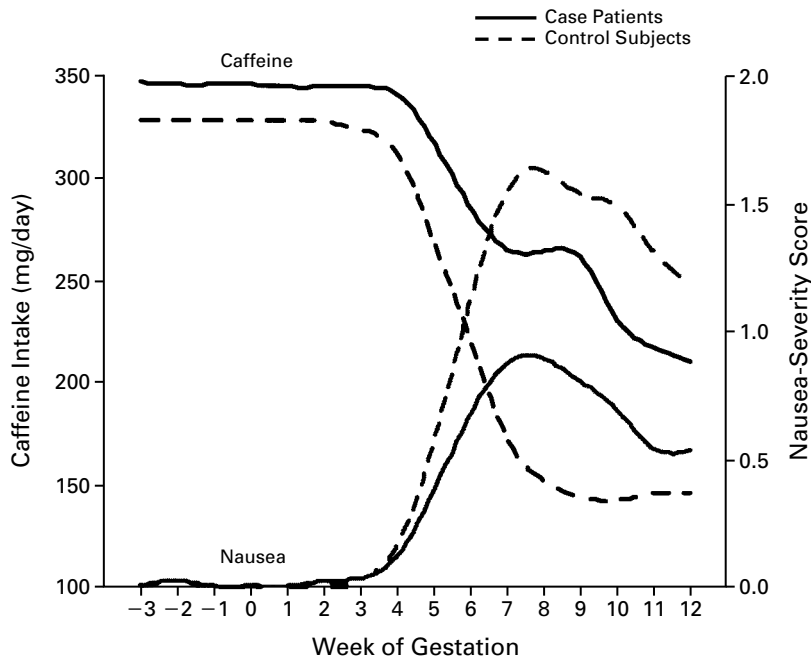


Figure 1. Mean Intake of Caffeine and Mean Severity of Nausea According to the Week of Gestation. Week 0 was the week of the last menstrual period. The case patients were women who had spontaneous abortion at 6 to 12 weeks of gestation. The control subjects did not have spontaneous abortion.

TABLE 2. ADJUSTED ODDS RATIOS FOR SPONTANEOUS ABORTION ASSOCIATED WITH THE INGESTION OF CAFFEINE DURING PREGNANCY AMONG SMOKERS AND NONSMOKERS.*

VARIABLE	SMOKERS		NONSMOKERS	
			THOSE WITH NO AVERSION TO COFFEE	NON-COFFEE DRINKERS
	odds ratio (95% CI)			
Daily intake of caffeine				
0-99 mg†	1.0	1.0	1.0	1.0
100-299 mg	0.9 (0.3-2.5)	1.3 (0.9-1.8)	1.8 (1.2-2.7)	1.7 (0.9-3.0)
300-499 mg	1.7 (0.6-4.6)	1.4 (0.9-2.0)	2.7 (1.7-4.5)	5.2 (0.8-33.4)
≥500 mg	0.7 (0.3-1.9)	2.2 (1.3-3.8)	4.1 (2.1-8.1)	—‡
P value	0.65	0.007	<0.001	0.007
No. of case patients/no. of control subjects	115/121	401/811	311/463	116/286

*Data on smoking status were missing for 46 case patients and 21 controls. The odds ratios have been adjusted for age; number of previous pregnancies; history of spontaneous abortion; consumption of alcohol during pregnancy (yes vs. no); and presence or absence of nausea, vomiting, and fatigue as symptoms of pregnancy. CI denotes confidence interval. The case patients were women who had spontaneous abortion at 6 to 12 weeks of gestation. The control subjects did not have spontaneous abortion.

†Women in this category served as the reference group.

‡The value could not be calculated because there were no such exposed control subjects.

The success rate of karyotyping was highly influenced by the week of gestation. In weeks 6 to 8, the fetal karyotype was known in only 25 percent of all spontaneous abortions (17 normal and 23 abnormal karyotypes), whereas in weeks 11 to 12, the corresponding figure was 57 percent (38 normal and 66 abnormal). The ingestion of caffeine was unrelated to the occurrence of spontaneous abortion of a fetus with an abnormal karyotype (Table 3). Among nonsmokers, the ingestion of a moderate or high level of caffeine was associated with an increased risk of spontaneous abortion of fetuses with normal as well as unknown karyotypes (Table 3). Among smokers, a high intake of caffeine was associated with an increased risk of spontaneous abortion of a fetus with a normal karyotype, but the confidence intervals were wide.

Our principal analyses were based on levels of caffeine ingestion that were averaged over the first trimester of pregnancy. When we disregarded caffeine intake and pregnancy-related symptoms during the last two completed weeks of gestation before the interview, the caffeine-related risk of spontaneous abortion of a fetus with a normal karyotype among non-

smokers was unchanged for moderate levels of ingestion of caffeine but was attenuated for the highest level of ingestion (at least 500 mg per day): odds ratio, 1.4 (95 percent confidence interval, 0.5 to 3.7).

DISCUSSION

Our results indicate that the ingestion of caffeine during early pregnancy is associated with an increased risk of first-trimester spontaneous abortion of a fetus with a normal karyotype and that the increase in risk associated with caffeine is consistently present only among nonsmokers. Our results also suggest that the finding of the association between caffeine ingestion and spontaneous abortion is not entirely a product of bias introduced by pregnancy-induced symptoms.^{6,7,14}

Measuring plasma cotinine allowed us to adjust for the misclassification of women according to smoking status. We found, in agreement with most previous studies,^{20,21} that smoking was associated with an increased risk of spontaneous abortion, but we were unable to detect an effect of caffeine among smokers. The effect of maternal smoking may conceal an effect of caffeine on the risk of spontaneous abortion. Al-

TABLE 3. ADJUSTED ODDS RATIOS FOR SPONTANEOUS ABORTION ASSOCIATED WITH THE INGESTION OF CAFFEINE DURING PREGNANCY AMONG NONSMOKERS AND SMOKERS, ACCORDING TO FETAL KARYOTYPE.*

VARIABLE	KARYOTYPE		
	ABNORMAL	NORMAL	UNKNOWN
Nonsmokers			
No. of case patients/no. of control subjects	115/811	74/811	212/811
odds ratio (95% CI)			
Daily intake of caffeine			
0-99 mg†	1.0	1.0	1.0
100-299 mg	1.0 (0.6-1.6)	2.0 (1.0-3.7)	1.5 (0.9-2.3)
300-499 mg	0.9 (0.5-1.7)	1.8 (0.8-3.8)	1.5 (0.9-2.4)
≥500 mg	1.8 (0.8-3.9)	2.2 (0.8-6.4)	2.6 (1.3-5.1)
P value	0.39	0.11	0.001
Smokers			
No. of case patients/no. of control subjects	29/121	20/121	66/121
odds ratio (95% CI)			
Daily intake of caffeine			
0-99 mg†	1.0	1.0	1.0
100-299 mg	1.4 (0.2-11.1)	0.5 (0.1-4.5)	0.7 (0.2-2.4)
300-499 mg	2.1 (0.3-15.9)	2.6 (0.4-16.7)	1.5 (0.5-4.7)
≥500 mg	0.5 (0.1-4.0)	1.9 (0.3-11.3)	0.5 (0.2-1.7)
P value	0.32	0.22	0.42

*Data on smoking status were missing for 46 case patients and 21 controls. The odds ratios have been adjusted for age; number of previous pregnancies; history of spontaneous abortion; ingestion of alcohol during pregnancy (yes vs. no); and presence or absence of nausea, vomiting, and fatigue as symptoms of pregnancy. CI denotes confidence interval. The case patients were women who had spontaneous abortion at 6 to 12 weeks of gestation. The control subjects did not have spontaneous abortion.

†The women in this category served as the reference group.

ternatively, because smoking increases the rate at which caffeine is eliminated,^{22,23} nonsmokers may be particularly susceptible to its effects. A possible interaction between caffeine and smoking with regard to the risk of spontaneous abortion has been suggested previously.¹³ A similar interaction between caffeine and smoking, with caffeine affecting primarily nonsmokers, has been reported with regard to the risk of delayed conception.²⁴ In contrast, caffeine has usually,^{25,26} but not always,²⁷ been associated with reduced fetal growth, primarily among smokers. The metabolism of caffeine is markedly slower in late pregnancy than in early pregnancy,²⁶ but the reasons for these differences in interactions between caffeine and smoking with respect to reproductive outcomes in early and late pregnancy remain speculative.

We probably limited both errors in the measurement of exposure by using face-to-face interviews close to the time of the spontaneous abortion in women who had such abortions and by matching the control subjects with the women with spontaneous abortion according to week of gestation. However, data on the ingestion of caffeine close to the time of spontaneous abortion could unintentionally include caffeine ingestion that occurred after fetal death, and such exposure should not be considered in a causal context.¹⁴ The most recent period for which caffeine ingestion was reported was the last completed week of gestation, thus there was an average of 3.5 days between the last measurement of caffeine ingestion and the time of spontaneous abortion.

The proportion of women who increased their intake of caffeine by at least 20 percent during the last two weeks of gestation was small (4 percent) in both the case and control groups, but we found that when the intake of caffeine during the last two weeks was not included in the analysis, the risk of spontaneous abortion of fetuses with normal karyotypes was reduced among nonsmokers. This analysis, hampered by limited statistical power, does not allow us to rule out the possibility of spurious positive results due to increased ingestion of caffeine among the case patients in response to lessening of the severity of symptoms. It is therefore reassuring that the ingestion of caffeine was unrelated to the spontaneous abortion of fetuses with abnormal karyotypes. The results of karyotyping were not known at the time of the interview, and the effect of systematic reporting errors would have applied equally to both fetal-karyotype groups. That the ingestion of caffeine did not influence the risk of spontaneous abortion of a fetus with an abnormal karyotype is in agreement with the lack of evidence regarding the potential mutagenicity of caffeine in humans. However, it is in contrast to the report that caffeine ingestion increased the risk of spontaneous abortions of fetuses with normal and abnormal karyotypes during the second trimester.¹⁰

Coffees brewed in Sweden have high concentrations

of caffeine as well as many other constituents,²⁸ and it is not known whether these constituents are possible risk factors for spontaneous abortion. The few studies, including our own, that have attempted to estimate the relative risks associated with caffeine from specific sources have had limited power.^{5,7,12,13} Nonetheless, our data suggest that caffeine from coffee has the same general effect as caffeine from other sources.

Our study corroborates many earlier reports that found an increased risk of spontaneous abortion among pregnant women who ingested caffeine.^{4,8,10,12,13} Recently, Klebanoff et al.⁹ reported that serum paraxanthine, a caffeine metabolite, was associated with an increased risk of spontaneous abortion only at very high concentrations (at or above the 95th percentile among the women they studied). Problems relating serum paraxanthine concentrations to caffeine intake, especially given the considerable variation among people in the rate of caffeine metabolism, make direct comparison of their results with ours impossible. However, their case group consisted mostly of women who had spontaneous abortions in the second trimester, and caffeine may be more detrimental in the first than in the second trimester, because the exposure of the fetus can be assumed to be greater in that period than later in the pregnancy.^{25,29}

Given the limitations of the current study, and the mixed results of previous studies, our findings should be interpreted cautiously. However, reducing caffeine intake during early pregnancy may be prudent.

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